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Multifocal Soft Tissue Sarcoma: Limb Salvage Following Hyperthermic Isolated Limb Perfusion With High-Dose Tumor Necrosis Factor and Melphalan

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Background and Objectives: The prognosis for recurrent multifocal limb soft tissue sarcoma (STS) is dismal due to systemic spread. However, many of these patients undergo amputation due to ineffective local control. The purpose of the present study was to determine whether isolated limb perfusion (ILP) with tumor necrosis factor (TNF) and melphalan permits limb salvage and palliation for such patients.

Methods: Of 53 STS patients treated with hyperthermic ILP with TNF (3–4 mg) and melphalan (1–1.5 mg/kg), 13 (25%) had multifocal STS and were candidates for amputation.

Results: The overall response rate was 92% (12/13) with 38% complete response and 54% partial response. Two patients died during the early postoperative period. Limb salvage was achieved in 85% of patients. One patient (8%) had only stable disease and underwent amputation. Local recurrence occurred in 38% but did not result in amputation.

Conclusions: Although the number of patients in this study is too small to allow definitive conclusions, it seems that ILP/TNF offer limb salvage and palliation for recurrent multifocal STS patients.

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KEY WORDS: **multifocal soft tissue sarcoma; isolated limb perfusion; tumor necrosis factor; melphalan**

INTRODUCTION

Multifocality has long been recognized as a grave prognostic sign in soft tissue sarcoma (STS), and its outcome is dismal, mainly due to systemic metastatic spread. However, these patients still require local control since the lesions tend to grow, protruding through the skin and invading adjacent structures, thus resulting in a non-functional, painful limb. Multifocal STS is refractory to most forms of conventional therapy. Limb sparing surgery is usually impossible due to the extent of disease. Even when complete resection is feasible, recurrence is common. Irradiation and chemotherapy have not proved beneficial in local control and palliation for such patients, making amputation sometimes inevitable [1]. This high failure rate has inspired the use of regional therapy techniques. The most effective regional therapy for advanced limb tumors is isolated limb perfusion (ILP). ILP enables the administration of chemotherapeutic agents at a dose of up to 20 times the maximally tolerated systemic dose. The high success rate observed in melanoma encouraged attempts to implement ILP in STS. However, using chemotherapeutic agents alone, only 25% response rates were observed [2–4].

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TABLE I. Patients

Patient no.	Sex/age (years)	Recurrent/primary	Histology	Location	No. of lesions	Prior therapy
1	F/32	Recurrent	Clear cell sarcoma	Leg	>50	Radiation + chemotherapy
2	M/78	Recurrent	MFH[a]	Leg	3	Radiation
3	M/22	Recurrent	Malignant schwanoma	Leg	2	Radiation + chemotherapy
4	M/73	Recurrent	Clear cell sarcoma	Forearm	10	None
5	M/76	Recurrent	MFH	Forearm	15	Radiation + chemotherapy
6	F/70	Primary	Epithelioid sarcoma	Ankle	4	None
7	F/72	Recurrent	Liposarcoma	Leg	2	Radiation + chemotherapy
8	M/76	Recurrent	MFH	Forearm	2	Radiation + chemotherapy
9	M/80	Recurrent	Leiomyosarcoma	Leg	>50	Radiation
10	F/70	Recurrent	Clear cell sarcoma	Leg	4	None
11	F/56	Recurrent	Liposarcoma	Forearm	3	Radiation
12	F/60	Recurrent	MFH	Leg	>30	Radiation + chemotherapy
13	F/79	Recurrent	MFH	Arm	10	None

[a]MFH, malignant fibrous histiocytoma.

The addition of recombinant tumor necrosis factor alpha (r-TNF-α) to the ILP led to a marked increase in the response rate for sarcoma [5,6]. TNF is known for its potent anti-neoplastic effect as demonstrated in various *in vitro* and *in vivo* studies. However, clinical implication has so far been impossible due to the septic shock-like syndrome leading to multiorgan failure which occurs immediately upon systemic administration of TNF [7].

ILP is an ideal setting for regional delivery of TNF while avoiding exposing the whole body to its lethal side effects. This approach has resulted in remarkable response rates for melanoma and non-resectable STS confined to the limb [5,6]. In this study, we evaluated its role in multifocal extremity STS.

MATERIALS AND METHODS

Between December 1992 and June 1997, 53 patients with STS were treated with TNF and melphalan via ILP. Thirteen of these patients had multifocal STS (Table I). There were 6 males and 7 females, with an age range of 22–80 years. Two patients underwent a double perfusion. All 13 patients had histologically proven high-grade STS confined to the limb, recurrent in 12 and primary in 1. Histologies were malignant fibrous histiocytoma (MFH) (5), clear cell sarcoma (3), liposarcoma (2), malignant schwanoma (1), epithelioid sarcoma (1), and leiomyosarcoma (1).

The number of lesions ranged from 2 to >50, and their size varied from 0.5 to 20 cm. Five tumors were located in the upper and 8 in the lower extremities. Twelve patients had had multiple previous surgical interventions, 9 had undergone irradiation, 6 systemic chemotherapy, and 1 ILP with adriamycin.

All patients were referred from the Unit for Orthopedic Oncology and all were considered absolute candidates for amputation. Staging studies were performed before each ILP/TNF. The study was conducted within the framework of an "Investigators Own Responsibility (IOR) Study," which was approved by the National Helsinki Committee. Informed consent was obtained from all patients.

Hyperthermic ILP With High-Dose r-TNF-α and Melphalan

The technique is described elsewhere [5]. Briefly, the main artery and vein of the perfused limb are dissected and all collaterals ligated. The vessels are cannulated and connected to a pump oxygenator similar to that used in cardiopulmonary bypass. A tourniquet (200–400 mmHg) or Esmark band is applied to the root of the limb to ascertain complete vascular isolation and to ensure that all tumors lie within the perfused area and receive adequate drug dosing.

The temperature of the perfused limb is maintained at 39–40°C during the entire procedure using both external heating and warming of the perfusate. Systemic leakage from the perfused limb is monitored continuously using ^{99}Tc-radiolabeled human serum albumin injected into the perfusate. Radioactivity above the precordial area is recorded using a Geiger counter.

Drugs

r-TNF-α (a gift from Boehringer-Ingelheim GmBH, Germany) was administered at a dose of 3 and 4 mg for the upper and lower limbs, respectively, as a bolus into the arterial line of the perfusate. Melphalan (Wellcome Bendix, Research Triangle Park, NC) was administered at 1.0 and 1.5 mg/kg body weight for the upper and lower limbs, respectively, 30 min after r-TNF-α and the perfusion was continued for a further 60 min.

Response Evaluation

Evaluation of response according to UICC criteria was performed 6–8 weeks after ILP. The lesions were counted and measured, and patients underwent multiple biopsies from the remaining tumors or tumor sites.

TABLE II. Results and Follow-Up*

Patient no.	Vascular approach	Response	Local recurrence	Systemic recurrence	Limb salvage	Dead/alive
1	Iliac	CR	—	+3 mo.	+	Died 4 mo.[a]
2	Iliac	PR	—	—	+	Died 1 mo.[b]
3	Femoral	PR				
2nd ILP	Iliac	SD	Amputation	+12 mo.	–	Died 18 mo.[a]
4	Brachial	PR	—	+8 mo.	+	Died 12 mo.[a]
5	Brachial	PR				
2nd ILP	Brachial	CR	+12 mo.	+34 mo.	+	Died 41 mo.[a]
6	Popliteal	PR	—	+20 mo.	+	Died 35 mo.[a]
7	Iliac	PR	Amputation	+30 mo.	–	Died 6 mo.[a]
8	Subclavian	CR	+9 mo.	+20 mo.	+	Died 27 mo.[a]
9	Iliac	CR	+8 mo.	+8 mo.	+	Died 10 mo.[a]
10	Iliac	PR	—	—	+	Died 3 mo.[a]
11	Brachial	PR	Amputation	—	–	Alive 8 mo.
12	Iliac	CR	—	—	+	Alive 8 mo.
13	Subclavian	PR	—	—	+	Died 7 weeks[b]

*CR, complete response; PR, partial response; SD, stable disease; mo., months.
[a]Sarcoma-related death.
[b]Postoperative death.

RESULTS

Fifteen ILP were performed in 13 patients via the external iliac (7), femoral (1), popliteal (1), brachial (4), and subclavian (2) vessels (Table II).

Complications

Local limb complications assessed according to Wieberdink et al. [8] manifested as redness in 8 (grade 2) and blisters in 4 (grade 3). No patient experienced neuropathy. One patient developed extensive necrosis necessitating eventual amputation. Mortality occurred in 2 patients, including one 78-year-old patient whose MFH was shown on postmortem to have almost completely regressed (>98% necrosis). The patient developed staphylococcal sepsis, which led to multiorgan failure and death 28 days after ILP. The second mortality was a 79-year-old female patient who developed aspiration pneumonia and multiorgan failure resulting in her death 7 weeks after the procedure.

Response

The overall response rate was 92% (12/13). Five patients had complete response (CR) (38%): 4 after a single perfusion and 1 after a double perfusion. Seven patients achieved partial response (PR) (54%). In 1 patient (8%), less than 50% of regression was observed. Limb sparing was achieved in 10 of 13 patients. Since the 2 patients who died some weeks following ILP had shown a significant response to the treatment, it was assumed that amputation would have been avoided had they survived. Three patients required amputation: 1 due to insufficient response, 1 to extensive necrosis of the tumor, and 1 in whom his remaining tumor was fixed to major blood vessels.

Within the limitations of a short follow-up period (4–41 months, median 16 months), and after excluding 2 patients due to early death and 3 patients who underwent amputation, local recurrence occurred in 3 of 8 patients (38%) within 8, 9, and 12 months. Systemic spread occurred in 8 of 11 patients (72%), and all of them died within 4–35 months.

DISCUSSION

Although of the same mesenchymal origin and sustaining resembling features, STS are extremely heterogenous. Among the subgroups are multifocal sarcomas that are defined as more than one lesion upon physical and/or pathological examination. Only a minority of STS patients have the multifocal type, which is found mainly in patients with recurrent, high-grade STS. The prognosis for this subgroup is poorer than that for patients with single tumors, with a higher tendency toward local failure and metastatic spread [9].

The multifocality makes complete resection less feasible and more patients will require amputation. The prognosis is dismal due to systemic microscopic spread of the sarcoma prior to surgery. This fact makes the extensive, mutilating surgery futile, since it diminishes quality of life without prolonging it. With this realization, we focused our attention on ILP/TNF as a palliative, limb sparing modality in multifocal STS patients. Despite improved results obtained by multimodality therapy, which has led to a significant reduction in amputation rates, 8.2% of extremity sarcoma patients still undergo amputation [10]. Indeed, hyperthermic ILP with high-dose TNF and melphalan results in a 90% response rate and 85% limb salvage [5,6].

The high rate of limb salvage is the most valuable and proven benefit of ILP with TNF and melphalan in advanced limb sarcoma patients; the marked tumor shrink-

age is the most important aspect of the treatment. The benefit of limb salvage is especially emphasized in patients with multiple sarcoma lesions. Despite the dismal prognosis, this subset of patients often requires local control; the lesions multiply, penetrate, and sometimes protrude through the skin and ulcerate. ILP performed in such patients is therefore the only option for limb salvage.

The overall response rate of 92% achieved is higher than the results obtained with standard treatments for STS. These results were obtained despite the fact that most patients had already failed previous chemotherapy and irradiation.

Two patients died in the immediate postoperative period due to complications not directly related to the treatment, but more to the procedure itself, which is a major operation. Both patients were elderly with coexisting cardiovascular problems. These factors, together with the fact that ILP/TNF is a palliative procedure in the multifocal STS group, might mandate more stringent inclusion criteria for this treatment in the elderly.

The experience with ILP using chemotherapeutic agents alone in advanced STS is limited, due to the low response rate [2–4,11,12]. Only anecdotal cases of CR have been described. The marked improvement in results in the current series is therefore attributed to the addition of TNF to the chemotherapeutics.

TNF exerts its anti-neoplastic effect through a variety of mechanisms. It has a direct cytolytic effect on several cancer cell lines, probably due to its ability to elicit apoptosis [13,14]. In vivo TNF activates secondary mediators. Its exogenous administration induces the generation of many cytokines, such as interleukin (IL)-1, IL-6, IL-8, interferon, and mediators such as oxygen free radicals, and arachidonic acid products [15,16].

The most prominent effect of TNF in vivo is attributed to its effect on the tumor's vasculature [17–19]. Using its procoagulant properties, TNF activates specific adhesion molecules, such as integrin $\alpha V\beta 3$, on the surface of endothelial cells [20] within the tumor and membranal receptors on macrophages and leukocytes. Rapid migration of leukocytes to the tumor's capillary bed, leading to adhesion to the endothelium, release of oxygen free radicals and other cytokines, and extensive local inflammatory reaction, may result in obstruction and destruction of the tumor's capillary bed. This TNF-induced endothelial damage is exclusive to tumor vasculature, whereas normal vasculature is spared.

TNF demonstrates only a mild anti-neoplastic activity when administered alone [21]. We assume that the addition of melphalan, which is synergistic to TNF [22], accounts for the late effect that we have observed in tumors, achieving a peak 6–8 weeks post-ILP.

It becomes evident that ILP with TNF and melphalan is an important modality for limb preservation in sarcoma patients [5,6]. The fact that limb preservation was achieved in almost all of our patients with multiple STS emphasizes its potential in these patients.

CONCLUSIONS

Even though the number of patients in this study is too small to allow definitive conclusions, it seems that ILP/TNF may offer limb salvage and palliation for recurrent multifocal STS patients.

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